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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/209,023	12/10/98	PATON V	P1256R3

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EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/209,023	Paton et al.
Examiner	**Group Art Unit**
Jennifer Nichols, Nee Hunt	1642

☒ Responsive to communication(s) filed on *Jul 11, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-9 and 12-33* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9 and 12-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Amendment

Acknowledgment is made of applicant's cancellation of claims 10-11. Claims 1-9 and 12-31 are pending in the application.

Claim Rejections Withdrawn

The provisional rejection of claims 1-19 under 35 U.S.C. 101 as claiming the same invention as Application No. 09/208,649 is withdrawn in light of applicant's amendment thereto.

The rejection of claims 1-33 under 35 U.S.C. 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention are withdrawn in light of applicant's amendments thereto.

The rejection of claims 1-13 under 35 U.S.C 102(a) as being anticipated by Baselga et al. (I) is withdrawn in light of the amendments thereto.

The rejection of claims 1-11 under 35 U.S.C 102(a) as being anticipated by Norton et al. is withdrawn in light of the amendments thereto.

The rejection of claims 1-5, 7-9, and 12 under 35 U.S.C 102(b) as being anticipated by Lippman et al. is withdrawn in light of the amendments thereto.

The rejection of claims 1-5, 7-9, and 12 under 35 U.S.C 102(b) as being anticipated by Hynes et al. is withdrawn in light of the amendments thereto.

The rejection of claims 1-5 and 12 under 35 U.S.C 102(b) as being anticipated by Arakawa et al. is withdrawn in light of the amendments thereto.

The rejection of claims 1-9 under 35 U.S.C. 103 (a) as being unpatentable over Hudkiak et al. is withdrawn in light of applicant's amendments thereto.

The rejection of claims 1-13 under 35 U.S.C. 103 (a) as being unpatentable over Baselga et al (II) in view of Hynes et al. is withdrawn in light of applicant's amendments thereto.

The rejection of claims 1-33 under 35 U.S.C. 103 (a) as being unpatentable over Baselga et al. (I) , Baselga et al (II), Norton, Lippman et al., Hynes et al., or Arakawa et al., in view of Singal at al., and further in view of Seifert et al. is withdrawn in light of applicant's amendments thereto.

Claim Rejections Maintained /New Grounds of Rejection

1. Claims 1-9 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al., Oncology, Vol 11, No 3, March 1997, Norton, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, Lippman et al, US Patent 5,578,482, November 26, 1996, Hynes et al. Biochemica et Biophysica Acta 1198, 1994, or Arakawa et al, US Patent 5,783,186, in view of Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995.

Baselga et al teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer,

comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (page 46 - page 47, column 1) The effective amount of the combination is less than the sum of the effective amounts of the chemotherapeutic agent and antibody individually (page 46, columns 1 and 3) The efficacy of this method is measured by time to disease progression (page 47, column 1).

Norton teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the HER2 extracellular domain, and a chemotherapeutic agent other than an anthracycline derivative, in the absence of an anthracycline derivative to a human patient. (See pages S10 8- S109, in the Patient Selection section and Table 1)

Lippman et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast, lung, ovarian, thyroid, salivary gland or prostate cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 epitope in the extracellular domain, and a chemotherapeutic agent. Lippman et al. further teaches various doses as effective to treat the corresponding cancer. Lippman et al. further teaches co-administration of "any chemotherapeutic" which would include non-anthracycline agents.(columns 9 and 26-29)

Hynes et al. teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the 4D5 extracellular domain, and a chemotherapeutic agent, cisplatin, which is not an anthracycline derivative. Further, Hynes teaches that the Antibody acts synergistically therefor the effective amount of the combination of antibody and chemotherapeutic agent is less than the sum of the effective amounts of the antibody and the chemotherapeutic agent individually. (page 178, column2, paragraph 1).

Arakawa et al. Teaches a method of treating human breast cancer which comprises administering an anti-ErbB2 antibody and a non-anthracycline chemotherapeutic agent, wherein coadministration enhances the therapeutic effect so that the effective amount is less than the effective amount of the antibody or chemotherapeutic agent when administered individually. (Column 5, line 66-column 6, line 29).

Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al fail to teach the specific chemotherapeutic agent Gemcitabine.

Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, teaches that as a chemotherapeutic, Gemcitabine has a higher response rate than many other chemotherapeutic agents and looks promising. (Page 2175, second column and table 8)

Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, teaches that Gemcitabine is an effective chemotherapeutic, and ideal for combination therapies(see for example, abstract)

Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, teaches that Gemcitabine is ideal for combination therapy and has low toxicity and high response rate (see for example, abstract).

Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, teaches that Gemcitabine is ideal for combination therapy and has low toxicity and high response rate (see for example, abstract).

Therefor it would have been primae facie obvious to select the specific non-anthracycline chemotherapeutic agent Gemcitabine in the combination therapies of Baselga et al., Norton, Lippman et al, Hynes et al, or Arakawa et al. and one would have been motivated to do so because Gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II).

2. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al., US Patent 5,770,195, and further in view of Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of

Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995..

Hudziak et al. teaches a method of treatment of any mammal diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically breast cancer, comprising administering and effective amount of an anti-ErbB2 antibody which binds the extracellular domain, and a chemotherapeutic agent which is not an anthracycline derivative. Hudziak fails to teach administration to humans or specific chemotherapeutic agent Gemcitabine.

Although Hudziak et al. is silent with respect to the administration of the therapy to human patients, humans would be encompassed by the scope of mammals and the therapy is clearly intended for human use, as the antibody binds a human cell receptor.

Further, Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teach the desirability of Gemcitabine because of it's low toxicity and high response rate as described supra.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to administer the therapy taught in Hudziak et al. to human patients, and one would have been motivated to do so because all receptors and cytotoxic factors are specific human factors and the treatment was ultimately intended for human use, as taught by Hudziak et al in the background of invention. Further, it would have been primae facie obvious to select the specific non-anthracycline chemotheraputic agent Gemcitabine in the combination therapies of Hudziak et al., and one would have been motivated to do so because Gemcitabine has low toxicity and a high

response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II).

3. Claims 1-9 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al, Journal of Clinical Oncology, Vol 14, No 3, March 1996, in view of Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995., and further in view of in view of Hynes et al, Biochimica et Biophysica Acta, 1994, page 178.

Baselga et al in Journal of Clinical Oncology teaches a method of treatment of a human patient diagnosed with a disorder characterized by over expression of ErbB2 receptor, specifically metastatic breast cancer, comprising administering an effective amount of an anti-ErbB2 antibody which binds the 4D5 extracellular domain (page 737, last paragraph). Time to response rate was used to measure efficacy (page 738, last paragraph). Although Baselga et al. fails to teach the administration of the antibody in combination with a chemotherapeutic to humans, it does teach that the antitumor effects of paclitaxel are potentiated by coadministration with the antibody and that this method is currently being administered to humans in clinical trials (page 743, last paragraph). Baselga et al further fails to teach that the effective amount of the

chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually and the selection of the specific chemotherapeutic agent Gemcitabine.

Hynes et al teaches that coadministration of an anti-ErbB2 antibody and a non-anthracycline derivative chemotherapeutic agent produces a synergistic treatment effect. Therefor the effective amount of the chemotherapeutic agent and the antibody are less than the effective amounts of those compounds administered individually.

Further, Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teach the desirability of Gemcitabine because of it's low toxicity and high response rate as described supra.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to administer the method of Baselga et al to human patients with a reasonable expectation of success and one would have been motivated to do so because administration of antibody is an effective method of treating metastatic breast cancer and coadministration of antibody and placitaxel enhanced anti-tumor effects, as taught by Baselga et al. Further, coadministration of antibody and chemotherapeutic agent produces a synergistic therapeutic response, as taught by Hynes et al. Further, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form the third composition that is to be used for the very same purpose: idea of combining them flows logically from their having been taught individually in the prior art." In re Kerkhoven (205 USPQ 1069, CCPA 1980). It is well known in the art as set forth above that anti-Her2 antibodies and the

chemotherapeutic placlitaxel are both useful for inhibiting the growth of tumors. Methods of inhibiting tumor growth by using chemotherapy are well established and therefor it would be obvious to use chemotherapy treatment in combination with an antibody therapy which has been established to be effective. Further, it would have been primae facie obvious to select the specific non-anthracycline chemotheraputic agent Gemcitabine in the combination therapies of Baselga et al.{II}, and one would have been motivated to do so because Gemcitabine has low toxicity and a high response rate and is ideal for combination therapy, as taught by Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II).

4. Claims 1-9 and 12-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al., Journal of Clinical Oncology, Vol 14, No 3, March 1996, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Baselga et al (II) and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. teaches as applied to claims 1-13 supra. Baselga and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of

manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Baselga et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

5. Claims 1-9 and 12-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselga et al., Oncology, Vol 11, No 3, March 1997, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Baselga et al and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teaches as applied to claims 1-13 supra. Baselga and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Baselga et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

6. Claims 1-9 and 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norton, Seminars in Oncology, Vol 24, No 4, Suppl 10, August 1997, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Norton and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teaches as applied to claims 1-11 supra. Norton and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Norton and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in

some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

7. Claims 1-5, 7-9, 12, and 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lippman et al, US Patent 5,578,482, November 26, 1996, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Lippman et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teaches as applied to claims 1-5, 7-9 and 12 supra. Lippman et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant,

including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Lippman et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

8. Claims 1-5, 7-9, 12, and 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hynes et al. Biochemica et Biophysica Acta 1198, 1994, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Hynes et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teaches as applied to claims 1-5, 7-9, and 12 supra. Hynes et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Hynes et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in

some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

9. Claims 1-5, 12, and 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa et al, US Patent 5,783,186, and Clemons et al., European Journal of Cancer, Volume 33, No. 13, pages 2171-2182, November 1997, Mosconi et al., European Journal of Cancer, Volume 33, Supl. 1, pages S14-S17, January 1997, Carmichael et al., European Journal of Cancer, Volume 33, Suppl 1, pages S27-S30, January 1997, or Carmicheal et al. Journal of Clinical Oncology, Vol. 13, No. 11, pages 2731-2736, November, 1995, in view of Singal at al., Journal of Molecular Cell Cardiology, Vol 27, 1995, and further in view of Seifert et al., The Annals of Pharmacology, Vol 28, September 1998.

Arakawa et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) teaches as applied to claims 1-5 and 12 supra. Arakawa et al. and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) fails to teach the corresponding articles of manufacture, including a warning not to administer the HER2 antibody with anthracycline derivatives and anthracycline-type chemotherapeutics, or when they are administered to administer with a cardioprotectant.

Articles of manufacture which comprise the reagents necessary to administer a particular treatment are well known in the art. Further, Singal et al. teaches that anthracycline derivatives are known to cause severe heart failure, thereby making anthracycline derivatives less desirable

than other chemotherapeutics. Singal further teaches that administration with a cardioprotectant, including probucol alleviates the risks of anthracycline administration (see abstract). Singal fails to teach the cardioprotectant dexrazoxane.

Seifert et al. teaches that the cardioprotectant dexrazoxane is useful as a cardioprotectant to alleviate the dangers of anthracycline therapy.(page 1063, conclusions)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the reagents necessary for the method taught by Arakawa et al.and Clemons et al., Mosconi et al., Carmichael et al. (I), or Carmicheal et al. (II) into a convenient kit form for the purposes of increased marketability convenience, reliability, and economy. Further it would be *prima facie* obvious to include a warning to avoid use of an anthracycline derivative, as these chemotherapeutics are known to cause fatal heart problems in some patients, or when they are administered to administer with a cardioprotectant. as taught by Singal et al. and Seifert et al.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that

sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

October 23, 2000

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